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BRIEF COMMUNICATION

Chronic Nicotine Treatment Potentiates Behavioral Responses to Dopaminergic Drugs in Rats

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SUEMARU, K., Y. GOMITA, K. FURUNO AND Y. ARAKI. *Chronic nicotine treatment potentiates behavioral responses to dopaminergic drugs in rats.* PHARMACOL BIOCHEM BEHAV **46**(1) 135–139, 1993.—In the present study, the behavioral effects of apomorphine, methamphetamine, and haloperidol were examined in nicotine-treated rats. All animals were SC administered nicotine at a dose of 0.5 mg/kg or saline once daily for 14 days. Hyperlocomotion induced by apomorphine (0.2 mg/kg, IP) and methamphetamine (1.0 mg/kg, IP) was greater in nicotine-treated rats than in control rats. Stereotyped behaviors induced by apomorphine (1.0 mg/kg, IP) and methamphetamine (5.0 mg/kg, IP) were also potentiated in nicotine-treated rats. However, the incidence of catalepsy induced by haloperidol (0.25–1.5 mg/kg, IP) was slightly lower in nicotine-treated rats. These results suggest that chronic nicotine treatment may increase the susceptibility of the dopaminergic system to dopaminergic drugs.

Nicotine Chronic treatment Methamphetamine Apomorphine Haloperidol Locomotor activity Catalepsy Stereotyped behavior

NICOTINE receptors are present at nigrostriatal and mesolimbic dopaminergic neurons (5), and nicotine increases the firing of dopaminergic neurons (2) and increases dopamine release (15,24). It has been reported that nicotine administration to rodents produces behavioral effects mediated in part by stimulation of nicotine receptors located on dopaminergic nerve terminals. For example, nicotine-induced hyperlocomotion is suppressed by a dopamine antagonist (17,21) and microinjection of nicotine into the nucleus accumbens or ventral tegmental area causes hyperlocomotion (21,22). On the other hand, repeated systemic administration of nicotine enhances nicotine-induced hyperlocomotion (3,4,6) and causes a tremor appearing only in the tail (12,13). However, there are few reports related to behavioral responses to dopaminergic drugs in rats chronically treated with nicotine. In the present study, to clarify the effect of chronic nicotine treatment on dopaminergic activity we examined apomorphine- and methamphetamine-induced hyperlocomotion and stereotyped behavior, as well as haloperidol-induced catalepsy, in chronically nicotine-treated rats.

METHOD

Animals

Male Wistar rats (supplied by Charles River Lab., Japan) weighing 200–250 g were kept in groups of five animals each in plastic-walled cages (26 × 36 × 25 cm) in a room with a 12 L : 12 D cycle (light on 0700–1900 h) at 22 ± 1°C and 60% relative humidity. Animals were allowed free access to food and water during the experiment.

Drugs and Administration

Drugs used consisted of nicotine free base solution (provided by the Smoking Research Foundation of Japan), apomorphine HCl powder (Sigma Chemical Co., St. Louis, MO), methamphetamine HCl powder (Dainiphon) and haloperidol HCl injection (Dainiphon). All drugs were dissolved in physiological saline.

All animals were SC administered nicotine at a dose of 0.5 mg/kg (nicotine-treated rats) or saline (control rats) once daily for 14 days. Apomorphine, methamphetamine, and haloperi-

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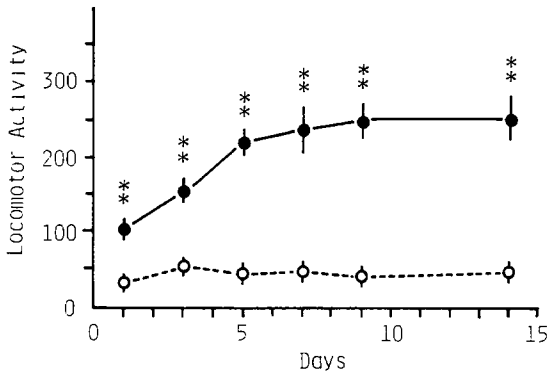

FIG. 1. Development of locomotor activity induced by daily administrations of nicotine in rats. Nicotine at a dose of 0.5 mg/kg or saline solution was SC administered once daily for 14 days. The number of blocks traversed (locomotor activity) in an open-field was counted immediately after nicotine administration. Each value represents the mean ± SEM for 15 min. (○), control rats (n = 6); (●), nicotine-treated rats (n = 6). **$p < 0.01$.

dol for the behavioral test were IP administered 24 h after the last injection of nicotine or saline. All drugs were administered in a volume of 0.1 ml per 100 g body weight.

Open-Field Test

Locomotor activity was measured using Hall's open-field apparatus (14), which was 60 cm in diameter with a gray-painted stainless steel wall 50 cm high. The field floor was divided into 19 blocks of almost similar area. The number of blocks traversed (locomotor activity) was counted. Locomotor activities induced by daily administration of nicotine were measured for 15 min immediately after administration on 1, 3, 5, 7, 9, and 14 days. Because the actions of hyperlocomotion induced by apomorphine and methamphetamine were longer than that of nicotine, the locomotor activities were measured for 30 min at 15 min after administration.

Stereotyped Behavior Test

Stereotyped behavior induced by apomorphine and methamphetamine was observed in the individual wire mesh cage (20 × 15 × 15 cm) and scored. The degree of stereotyped behavior was measured as follows; 0, no stereotype; 1, discontinuous sniffing; 2, continuous sniffing; 3, continuous sniffing and discontinuous licking or biting; 4, continuous sniffing and continuous licking or biting.

Catalepsy Test

Catalepsy induced by haloperidol was measured using the bar test (26). The rear feet of animals were placed on a platform 30 min after haloperidol administration and their front feet on a horizontal bar suspended 12 cm above the platform. The duration of catalepsy produced was measured. When the duration time was more than 30 s, catalepsy was judged to be present.

Statistical Analysis

The locomotor activity when nicotine was daily administered was analyzed by an analysis of variance (ANOVA) with two factors. The intragroup comparisons for hyperlocomotion and stereotyped behavior induced by apomorphine and methamphetamine were made by the two-tailed Mann–Whitney U-test and the incidence of catalepsy induced by haloperidol was analyzed by Fisher's exact probability test.

RESULTS

The development of locomotor activity induced by daily administration of nicotine at a dose of 0.5 mg/kg is shown in Fig. 1. Administration of nicotine on the first day significantly increased locomotor activity as compared with saline control rats (U = 0, $p < 0.01$). The stimulating effect of nicotine was further enhanced by daily administration. There were significant differences in values to drug treatment effect between nicotine-treated rats and control rats, $F(1, 60) = 218.6$, $p < 0.001$, and also in values to the effect of daily nicotine treat-

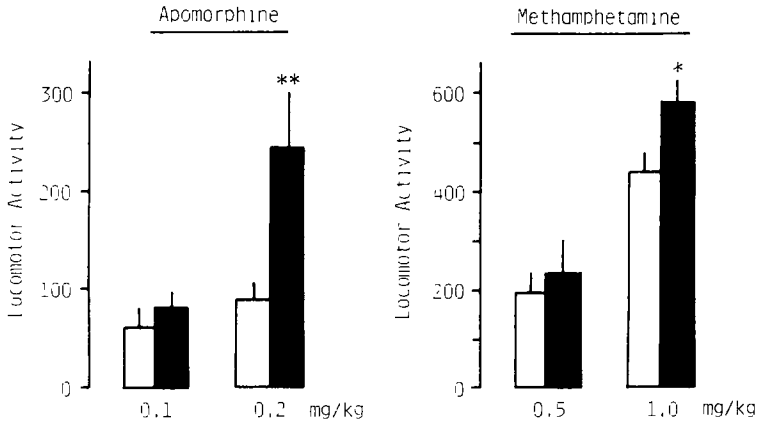

FIG. 2. Locomotor activity induced by apomorphine or methamphetamine in rats chronically treated with nicotine or saline. All animals were SC administered nicotine at a dose of 0.5 mg/kg or saline once daily for 14 days. Apomorphine and methamphetamine were IP administered 24 h after the last injection of nicotine or saline. Each value represents the mean number of blocks traversed (locomotor activity) for 30 min in an open-field. The vertical bars show the SEM. (□), control rats (n = 5); (■), nicotine-treated rats (n = 6). *$p < 0.05$, **$p < 0.01$.

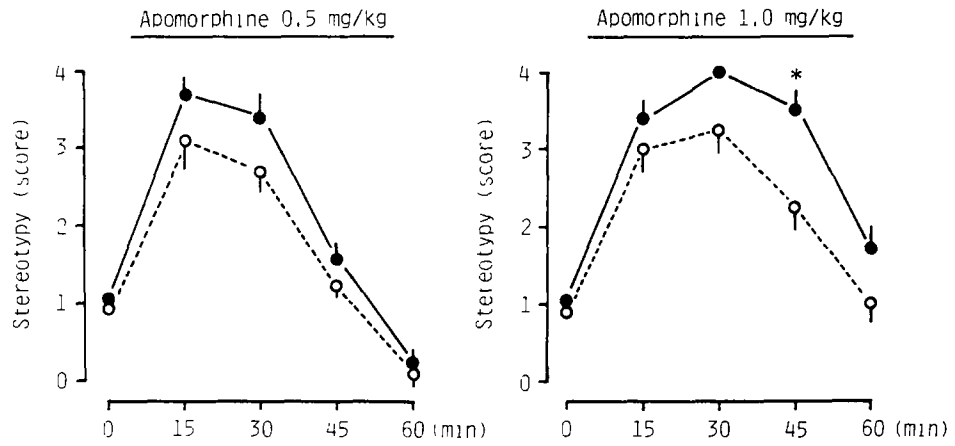

FIG. 3. Stereotyped behavior induced by apomorphine in rats chronically treated with nicotine or saline. All animals were SC administered nicotine at a dose of 0.5 mg/kg or saline once daily for 14 days. Apomorphine was IP administered 24 h after the last injection of nicotine or saline. Each point represents the mean score ± SEM. (○), control rats (n = 8); (●), nicotine-treated rats (n = 8). *$p < 0.05$.

ment in the nicotine-treated group, $F(5, 25) = 6.84$, $p < 0.001$.

Figure 2 shows hyperlocomotion induced by apomorphine at doses of 0.1 and 0.2 mg/kg or methamphetamine 0.5 and 1.0 mg/kg in nicotine-treated or control rats. Hyperlocomotion induced by apomorphine at a dose of 0.2 mg/kg and by methamphetamine at a dose of 1.0 mg/kg was greater in nicotine-treated rats than in control rats. There were significant differences between apomorphine- or methamphetamine-treated groups and each corresponding control ($U = 0$, $p < 0.01$; $U = 6$, $p < 0.05$, respectively).

Administration of apomorphine at doses of 0.5 and 1.0 mg/kg, or methamphetamine at doses of 5 and 10 mg/kg, caused marked stereotyped behavior, and its maximum effects were observed 15–30 min after apomorphine administration (Fig. 3) and 1–2 h after methamphetamine administration (Fig. 4). The scores of stereotyped behavior induced by apomorphine (0.5 and 1.0 mg/kg) in nicotine-treated rats were higher than those in control rats. The scores of stereotyped behavior induced by methamphetamine at a dose of 5 mg/kg were also markedly increased in nicotine-treated rats. However, the scores in rats administered methamphetamine at a dose of 10 mg/kg were only slightly higher than those in control rats because the score had already reached the maximum value.

The incidence of catalepsy induced by haloperidol at doses of 0.1–1.0 mg/kg in control rats increased in a dose-dependent manner, and administration of 1 mg/kg caused the catalepsy in all rats (Fig. 5). The ED_{50} value for catalepsy in control rats was 0.40 mg/kg. On the other hand, the incidence of haloperidol-induced catalepsy in nicotine-treated rats was lower than that in control rats. The ED_{50} value for catalepsy in nicotine-treated rats was 0.70 mg/kg. However, there was no significant difference between both groups.

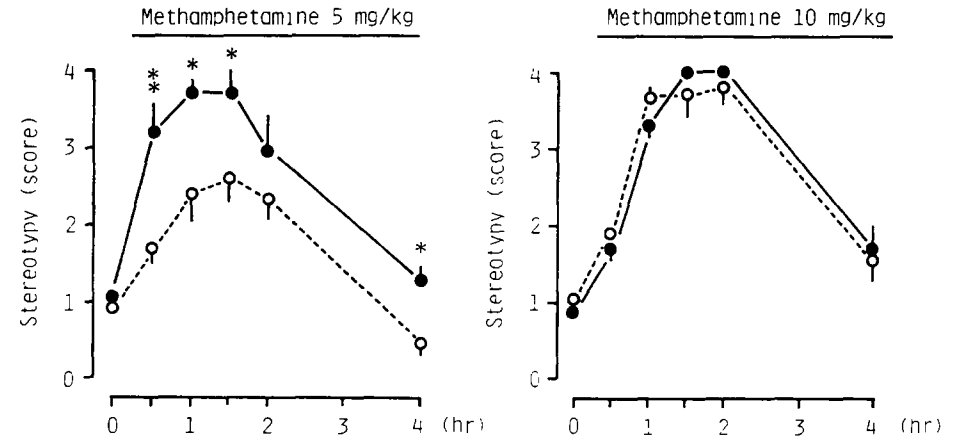

FIG. 4. Stereotyped behavior induced by methamphetamine in rats chronically treated with nicotine or saline. All animals were SC administered nicotine at a dose of 0.5 mg/kg or saline once daily for 14 days. Methamphetamine was IP administered 24 h after the last injection of nicotine or saline. Each point represents the mean score ± SEM. (○), control rats (n = 7); (●), nicotine-treated rats (n = 7). *$p < 0.05$, **$p < 0.01$.

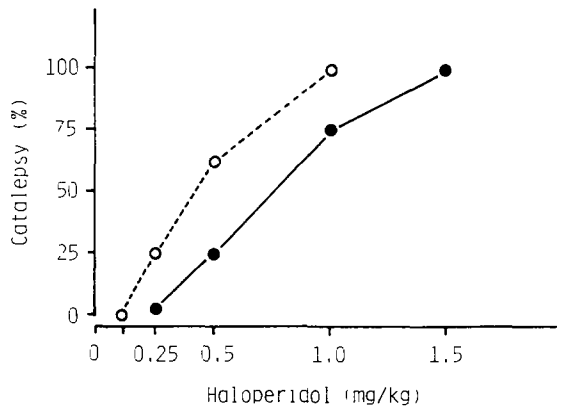

FIG. 5. Haloperidol-induced catalepsy in rats chronically treated with nicotine or saline. All animals were SC administered nicotine at a dose of 0.5 mg/kg or saline once daily for 14 days. Haloperidol was IP administered 24 h after the last injection of nicotine or saline. Each point represents the percentage incidence of catalepsy. (○), control rats (n = 8); (●), nicotine-treated rats (n = 8).

DISCUSSION

It has been reported that administration of nicotine stimulates or depresses locomotor activity depending on the dose and genetic nature of the animal (8,19). In addition, both suppression (tolerance) and enhancement of nicotine-induced hyperlocomotion have been reported after repeated systemic administration (3,4,16,20). In the present study, nicotine was administered to rats at a dose of 0.5 mg/kg once daily. This dose of nicotine stimulated locomotor activity, which was enhanced by repeated administration. On the other hand, hyperlocomotion induced by acute administration of nicotine is associated with dopaminergic activation in the striatum or mesolimbic system (1,9) but enhancement of the stimulating effect by chronic administration is associated with an increase in the number of dopaminergic receptors (10,11) and a decrease of dopamine turnover in the rat brain (11,16,18). Therefore, the increased hyperlocomotion and stereotyped behavior induced by methamphetamine and apomorphine in chronically nicotine-treated rats may be due to an increased number of dopaminergic receptors.

In acute continuous nicotine infusion with an osmotic minipump for 1 day, the stimulating effect of amphetamine on locomotor activity is attenuated but that of apomorphine is not (9). Further, in chronic nicotine infusion with an osmotic minipump for 14 days both apomorphine- and amphetamine-induced stimulations of locomotor activity are potentiated (11). In the present study, chronic systemic injection of nicotine also enhanced the locomotor activity and stereotyped behavior induced by apomorphine and methamphetamine. These findings suggest that dopaminergic neuronal activity in nicotine-treated animals is affected by the duration of exposure to the drug.

It has been reported that acute administration of nicotine potentiates haloperidol-induced catalepsy and hypoactivity in rats (7). However, in the present study haloperidol-induced catalepsy was slightly decreased in chronic nicotine-treated rats. This suggests that chronic nicotine administration causes tolerance to the haloperidol effect. Concerning this tolerance, Prasad et al. (23) reported that chronic nicotine administration blocks increases in the D_2 dopamine receptor density in the rat striatum induced by repeated administration of haloperidol. Therefore, the decreased catalepsy in nicotine-pretreated rats might be due to changes in the dopaminergic receptor system.

In conclusion, the present study indicates that chronic systemic administration of nicotine potentiates locomotor activity and stereotyped behavior induced by apomorphine and methamphetamine. These findings suggest that chronic nicotine treatment increases reaction to dopaminergic drugs.

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